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### Authors

Jansen, Willemijn J  
Ossenkoppele, Rik  
Knol, Dirk L  
et al.

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## Original Investigation

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# Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia A Meta-analysis

Willemijn J. Jansen, MSc<sup>1</sup>; Rik Ossenkoppele, PhD<sup>2,3,4,5</sup>; Dirk L. Knol, PhD<sup>6</sup>; [et al](#)

[Author Affiliations](#) [Article Information](#)

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## Abstract

**Importance** Cerebral amyloid- $\beta$  aggregation is an early pathological event in Alzheimer disease (AD), starting decades before dementia onset. Estimates of the prevalence of amyloid pathology in persons without dementia are needed to understand the development of AD and to design prevention studies.

**Objective** To use individual participant data meta-analysis to estimate the prevalence of amyloid pathology as measured with biomarkers in participants with normal cognition, subjective cognitive impairment (SCI), or mild cognitive impairment (MCI).

**Data Sources** Relevant biomarker studies identified by searching studies published before April 2015 using the MEDLINE and Web of Science databases and through personal communication with investigators.

**Study Selection** Studies were included if they provided individual participant data for participants without dementia and used an a priori defined cutoff for amyloid positivity.

**Data Extraction and Synthesis** Individual records were provided for 2914 participants with normal cognition, 697 with SCI, and 3972 with MCI aged 18 to 100 years from 55 studies.

**Main Outcomes and Measures** Prevalence of amyloid pathology on positron emission tomography or in cerebrospinal fluid according to AD risk factors (age, apolipoprotein E [*APOE*] genotype, sex, and education) estimated by generalized estimating equations.

**Results** The prevalence of amyloid pathology increased from age 50 to 90 years from 10% (95% CI, 8%-13%) to 44% (95% CI, 37%-51%) among participants with normal cognition; from 12% (95% CI, 8%-18%) to 43% (95% CI, 32%-55%) among patients with SCI; and from 27% (95% CI, 23%-32%) to 71% (95% CI, 66%-76%) among patients with MCI. *APOE*- $\epsilon$ 4 carriers had 2 to 3 times higher prevalence estimates than noncarriers. The age at which 15% of the participants with normal cognition were amyloid positive was approximately 40 years for *APOE* $\epsilon$ 4 $\epsilon$ 4 carriers, 50 years for  $\epsilon$ 2 $\epsilon$ 4 carriers, 55 years for  $\epsilon$ 3 $\epsilon$ 4 carriers, 65 years for  $\epsilon$ 3 $\epsilon$ 3 carriers, and 95 years for  $\epsilon$ 2 $\epsilon$ 3 carriers. Amyloid positivity was more common in highly educated participants but not associated with sex or biomarker modality.

**Conclusions and Relevance** Among persons without dementia, the prevalence of cerebral amyloid pathology as determined by positron emission tomography or cerebrospinal fluid findings was associated with age, *APOE* genotype, and presence of cognitive impairment. These findings suggest a 20- to 30-year interval between first development of amyloid positivity and onset of dementia.

## Introduction

Alzheimer disease (AD) is the most common cause of dementia, with a worldwide prevalence of about 25 million in 2010, expected to be doubled by 2030 because of increased life expectancy.<sup>1</sup> The earliest recognizable pathological event in AD is cerebral amyloid- $\beta$  aggregation.<sup>2</sup> This pathology may be present up to 20 years before the onset of dementia.<sup>3,4</sup> Novel research criteria for AD in individuals without dementia emphasize the presence of amyloid pathology to define the first stage of the disease.<sup>5,6</sup>

Prevalence estimates of amyloid pathology in persons without dementia are needed to better understand the development of AD and to facilitate the design of AD prevention studies. Initiation of treatment for AD in the prodementia phase, when neuronal damage is still limited, may be crucial to have clinical benefit.<sup>7</sup> Neuropathological studies have reported prevalences of amyloid pathology in nondemented individuals ranging between 10% and 60%.<sup>8,9</sup> Studies that assessed amyloid pathology in nondemented individuals during life using biomarkers in cerebrospinal fluid (CSF) or on positron emission tomography (PET) also showed large variability in prevalence estimates (10%-70%).<sup>10-13</sup> This variability may have resulted from small sample sizes, differences in study design, and participant selection.

The aim of this study was to estimate the prevalence of amyloid pathology as assessed by biomarkers in nondemented individuals with an individual participant meta-analysis. We estimated the prevalence in participants with normal cognition, subjective cognitive impairment (SCI), and mild cognitive impairment (MCI) and investigated the relation with known risk factors for AD-type dementia, including age, sex, education, and *APOE* genotype. We also tested the association of biomarker modality and recruitment strategies with prevalence estimates and compared age-specific estimates of amyloid positivity in participants with normal cognition with the prevalence of AD-type dementia in the general population.

## Methods

To identify relevant biomarker studies, the MEDLINE and Web of Science databases were searched for studies published before April 2015. The search terms used for PET studies were *PET* and (*Pittsburghor PiBor florbetapiror AV-45or florbetabenor flutemetamol*) and (*amyloidor abeta*). The search terms used for CSF studies were (*CSF* for *cerebrospinal fluid*) and (*amyloidor abeta*). Titles and abstracts were reviewed and relevant studies were retrieved. Searches were restricted to articles published in the English language. Studies were included if amyloid biomarker data for participants without dementia were reported and an a priori defined cutoff for amyloid abnormality was used. Studies that included participants with neurological, psychiatric, or other diseases that might affect the central nervous system were excluded. We also asked partners from 2 European multicenter collaborative projects, BIOMARKAPD and EMIF-AD, to provide unpublished data (Figure 1).

As most published studies did not provide prevalence estimates according to age and other risk factors, we asked study contact persons to provide participant-level data or tabulated data according to 10-year age categories and unpublished data if available. Tabulated data were converted to participant-level data with the average age in the age category. The quality of primary articles from each study was systematically assessed using relevant criteria from the STROBE<sup>14</sup> and QUADAS<sup>15</sup> guidelines (eTable 1 in the Supplement). All participants gave written informed consent to participate. Studies were approved by the local ethics committees of the participating centers.

## Data Collection and Operationalization

Information on study procedures was extracted from the publication or requested from the study contact person and used to create a common set of variables.

### Cognitive Status, *APOE*, Sex, and Education

Normal cognition was defined as normal scores on cognitive tests, the absence of cognitive complaints for which medical help was sought, or both. Subjective cognitive impairment was defined as presence of a cognitive complaint with presentation at a health care facility but normal cognition on tests. Mild cognitive impairment was defined according to published criteria.<sup>16,17</sup> These include a decline in memory or another cognitive domain reported by the patient, informant, or both and objectively verified by neuropsychological testing, in combination with no or minimal impairment in activities of daily living and not meeting criteria for dementia. Mild cognitive impairment was subclassified as amnesic MCI or nonamnesic MCI when possible. Information on *APOE*- $\epsilon$ 4 carrier status (yes/no), *APOE* genotype, and years of education was retrieved. To describe the association of *APOE* genotype with age, we reported for each genotype the age at which 15% of the participants with normal cognition were amyloid positive as a proxy for first appearance of abnormal amyloid.

### Setting and Recruitment

The study setting was classified as clinical if patients presented with cognitive complaints at a health care facility; research if patients were asked to participate in research by recruitment through advertisements or

from other hospital departments; population-based if a random sample of the general population was included; or mixed if participants were recruited from a combination of settings.

## Amyloid Assessment

Measurement details documented included amyloid tracer and assessment via visual scales or quantitative measures for PET studies and assay used to measure amyloid- $\beta_{1-42}$  levels for CSF studies. Positron emission tomography and CSF biomarkers were dichotomized as negative (normal) or positive (abnormal) according to study-specific cutoffs. (See eTables 2 and 3 in the [Supplement](#) for measurement details.) For participants who had both PET and CSF amyloid measures, we selected the first amyloid measure in time.

## Comparison With Prevalence of AD-Type Dementia

Age- and *APOE*-specific prevalence data of AD-type dementia were obtained through a meta-analysis or from published lifetime risk data for AD-type dementia<sup>18</sup> as described in the eMethods in the [Supplement](#).

## Number Needed to Screen

To use the prevalence estimates in selecting participants at risk for amyloid positivity for AD prevention studies, numbers needed to screen to identify 1 amyloid-positive participant were calculated as described in the footnote of eTable 6 in the [Supplement](#).

## Statistical Analysis

We conducted a meta-analysis with individual participant data, in which original research data were sought directly from study contact persons, combined, and reanalyzed centrally. Generalized estimating equations (GEEs) were used to estimate the prevalence and odds ratios (ORs). Generalized estimating equations allow for analysis of binary correlated data such that participant-level data on the prevalence from all studies could be modeled while simultaneously accounting for the clustering of participants within studies. We assumed a logit link function for binary outcome with an exchangeable correlation structure to account for within-study correlation. Analyses were performed using SPSS version 20.0 (IBM) with the `genlin` command. They were conducted using the total study population unless specified otherwise.

The main analyses were performed with cognitive status (normal cognition, SCI, MCI), age, sex, education, and *APOE*- $\epsilon 4$  genotype as independent variables. Age was entered as a continuous measure centered at the median. Educational level was dichotomized at the median (high,  $\geq 14$  years, vs moderate to low,  $< 14$  years). Secondary analyses tested associations with biomarker modality, MCI subtype, published vs unpublished studies, setting, and recruitment strategy while adjusting for cognitive status, age, and *APOE*- $\epsilon 4$  carrier status. We tested 2-way and 3-way interactions between variables and age as a quadratic term, and these were retained in the equation in case of a significant Wald statistic as indicated in table footers and figure legends. Analyses were repeated using natural cubic splines with knots at ages 50, 60, 70, and 80 years, but this did not improve the model. Estimated probabilities and 95% confidence intervals from the

GEE analyses were used in tables. Probabilities estimated by GEE were compared with the observed probabilities in 5-year age groups.

The extent of between-study variability was investigated in several ways. In the total sample, the random intercept variance related to study was estimated in a random-effects analysis with the independent variables age, *APOE*- $\epsilon$ 4 carrier status, cognitive status, and interactions using the *xtmelogit* function from Stata version 12.0 (StataCorp). This variance was expressed as an intraclass correlation coefficient. In diagnostic and *APOE* subgroups, heterogeneity within 5-year age strata was assessed with the  $I^2$  statistic<sup>19</sup> from a random-effects meta-analysis in Stata version 12.0. An  $I^2$  statistic value greater than 50% was considered indicative for substantial heterogeneity.<sup>19</sup> Center variability across the age range was visualized by plotting the prevalence for studies with more than 50 participants.

Significance level was set at  $P < .05$  in 2-sided tests, uncorrected for multiple comparisons. When associations changed after correcting for multiple comparisons with the Bonferroni method, this was mentioned in the text or table. R version 3.1.2 (R Foundation for Statistical Computing) and GraphPad Prism version 6.0 (GraphPad Software) were used for graphs with estimated probabilities and 95% confidence intervals from the GEE analyses.

## Results

The literature search resulted in 7578 publications; amyloid was assessed by PET in 890 and by CSF in 6688. From these, 599 were selected for full-text review. We identified 47 studies from the European multicenter projects (Figure 1). A total of 91 unique studies met inclusion criteria; the authors of 55 studies agreed to share data. Contact persons from 54 studies provided participant-level data and 1 provided tabulated data ( $n = 137$ ). Of the 36 studies for which contact persons refused or did not reply, 31 were selected through the literature search and 5 from the European multicenter studies. Characteristics of the 31 excluded published studies did not differ from those of the 55 included studies (eTable 4 in the Supplement).

### Study Characteristics

Of the selected studies, 45 were single-center and 10 were multicenter studies. (eTable 5 in the Supplement shows detailed study information.) Forty-one studies provided data for participants with normal cognition, 20 for patients with SCI, and 47 for patients with MCI. Of the MCI studies, 8 classified patients with MCI as amnesic MCI or nonamnesic MCI, 10 studies only included patients with amnesic MCI, and all other studies used a broad MCI definition or did not specify MCI subtype. Information on *APOE*- $\epsilon$ 4 carrier status was provided by 41 studies and information on *APOE* genotype by 37 studies. All studies but 1 specified the sex of the participants. Information on years of education was available from 44 studies. Studies contributing data for participants with normal cognition were performed in a research setting in 95% ( $n = 39$ , selection through advertisements in 15, from hospitals in 10, and from other or unknown sources in 14) and a mixed setting in 5% ( $n = 2$ ). Forty-six of the studies (98%) that included patients with SCI or MCI were performed in a clinical setting.

Amyloid-PET data were provided by 29 studies. Of these, 22 studies used [ $^{11}\text{C}$ ]Pittsburgh compound-B (PiB), 9 [ $^{18}\text{F}$ ]florbetapir, 2 [ $^{18}\text{F}$ ]florbetaben, and 1 [ $^{18}\text{F}$ ]flutemetamol, including 5 that used multiple tracers. Eleven studies assessed the PET images by visual scales whereas 16 studies used quantitative assessment and 2 studies used both methods. Cerebrospinal fluid amyloid- $\beta_{1-42}$  data were provided by 31 studies. The Innotech enzyme-linked immunosorbent assay (Fujirebio Europe) was used for CSF analysis in 29 studies and the xMAP Luminex assay in 2 studies. Two studies (1111 participants) provided data on both PET and CSF amyloid measures. Primary studies were assessed with the quality rating criteria, and typically met all criteria, although bias could not be assessed in 37 publications and participant flow remained unclear in 2 publications (eTable 1 in the [Supplement](#)).

## Participant Characteristics

We included 7583 participants from 55 studies, of whom 2914 (38%) had normal cognition, 697 (9%) SCI, and 3972 (52%) MCI. Amyloid positivity was assessed with PET for 2370 participants (31%; 1346 normal cognition, 35 SCI, 989 MCI) and with CSF for 5213 participants (69%; 1568 normal cognition, 662 SCI, 2983 MCI). Baseline characteristics according to cognitive status are shown in [Table 1](#). Participants with missing *APOE* data did not differ in amyloid positivity and sex from participants with *APOE* data but more often had limited education (63%) compared with participants who had these data available (48%,  $\chi = 62.5$ ,  $P < .001$ ). Participants with missing sex or education data did not differ in amyloid positivity, sex or education, and *APOE*- $\epsilon 4$  carrier status from participants with these data.

## Prevalence of Amyloid Positivity

Estimated probabilities of amyloid positivity according to cognitive status, *APOE*- $\epsilon 4$  status, and age are displayed in [Figure 2](#), [Figure 3A](#) and [B](#), and [Table 2](#). Observed prevalence estimates are shown in [Table 3](#). The difference between the observed and predicted prevalence rates was less than 10% in more than 90% of the comparisons indicating good model fit. Amyloid positivity was about twice as common in patients with MCI compared with participants with normal cognition (mean difference, 25% [95% CI, 22% to 28%];  $P < .001$ ) or SCI (mean difference, 23% [95% CI, 14% to 32%];  $P < .001$ ), while it did not differ between participants with normal cognition and SCI (mean difference, 2% [95% CI, -6% to 10%];  $P = .62$ ). Amyloid positivity increased with age in all diagnostic groups.

*APOE*- $\epsilon 4$  carriers had 10% to 40% higher absolute prevalence estimates than noncarriers in each diagnostic group ([Table 2](#), [Figure 3A](#) and [B](#)). At the median age of 70 years, the prevalence estimates were different between all *APOE* genotypes in participants with normal cognition, except for those of the  $\epsilon 2\epsilon 4$  and  $\epsilon 3\epsilon 4$  genotypes, which did not differ from each other (mean difference  $\epsilon 4\epsilon 4$  vs  $\epsilon 3\epsilon 4$ , 38% [95% CI, 22% to 53%];  $P < .001$ , vs  $\epsilon 2\epsilon 4$ , 28% [95% CI, 7% to 49%];  $P = .008$ , vs  $\epsilon 3\epsilon 3$ , 60% [95% CI, 44% to 75%];  $P < .001$ , vs  $\epsilon 2\epsilon 3$ , 73% [95% CI, 58% to 87%];  $P < .001$ ; mean difference  $\epsilon 3\epsilon 4$  vs  $\epsilon 2\epsilon 4$ , 9% [95% CI, -1% to 20%];  $P = .08$ , vs  $\epsilon 3\epsilon 3$ , 22% [95% CI, 18% to 26%];  $P < .001$ , vs  $\epsilon 2\epsilon 3$ , 35% [95% CI, 29% to 40%];  $P < .001$ ; mean difference  $\epsilon 2\epsilon 4$  vs  $\epsilon 3\epsilon 3$ , 31% [95% CI, 21% to 42%];  $P < .001$ , vs  $\epsilon 2\epsilon 3$ , 44% [95% CI, 31% to 57%];  $P < .001$ ; mean difference  $\epsilon 3\epsilon 3$  vs  $\epsilon 2\epsilon 3$ , 13% [95% CI, 8% to 17%];  $P < .001$ ) ([Figure 3C](#)).

After correction for multiple comparisons,  $\epsilon 2\epsilon 4$  and  $\epsilon 4\epsilon 4$  showed no statistically significant difference ( $P = .08$ ). None of the 10 participants with  $\epsilon 2\epsilon 2$  were amyloid positive. *APOE* genotype was associated with the age at onset of amyloid positivity. For example, the age at which 15% of the participants with normal cognition were amyloid positive was approximately 40 years for  $\epsilon 4\epsilon 4$  carriers, 50 years for  $\epsilon 2\epsilon 4$  carriers, 55 years for  $\epsilon 3\epsilon 4$  carriers, 65 years for  $\epsilon 3\epsilon 3$  carriers, and 95 years for  $\epsilon 2\epsilon 3$  carriers. In patients with SCI, prevalence of amyloid pathology according to *APOE* genotype was similar to participants with normal cognition in all age groups (mean difference, 1% [95% CI, -11% to 12%];  $P = .92$ ). In patients with MCI, the prevalence differed between genotypes at the median age of 70 years, while again the  $\epsilon 2\epsilon 4$  and  $\epsilon 3\epsilon 4$  genotypes did not differ from each other; the difference between the  $\epsilon 2\epsilon 4$  and  $\epsilon 3\epsilon 3$  genotypes was not statistically significant (mean difference  $\epsilon 4\epsilon 4$  vs  $\epsilon 3\epsilon 4$ , 23% [95% CI, 17% to 29%];  $P < .001$ , vs  $\epsilon 2\epsilon 4$ , 33% [95% CI, 14% to 51%];  $P = .001$ , vs  $\epsilon 3\epsilon 3$ , 54% [95% CI, 47% to 60%];  $P < .001$ , vs  $\epsilon 2\epsilon 3$ , 64% [95% CI, 57% to 71%];  $P < .001$ ; mean difference  $\epsilon 3\epsilon 4$  vs  $\epsilon 2\epsilon 4$ , 10% [95% CI, -9% to 28%];  $P = .31$ , vs  $\epsilon 3\epsilon 3$ , 31% [95% CI, 25% to 37%];  $P < .001$ , vs  $\epsilon 2\epsilon 3$ , 41% [95% CI, 34% to 48%];  $P < .001$ ; mean difference  $\epsilon 2\epsilon 4$  vs  $\epsilon 3\epsilon 3$ , 21% [95% CI, -1% to 43%];  $P = .06$ , vs  $\epsilon 2\epsilon 3$ , 31% [95% CI, 9% to 53%];  $P = .005$ ; mean difference  $\epsilon 3\epsilon 3$  vs  $\epsilon 2\epsilon 3$ , 10% [95% CI, 6% to 14%];  $P < .001$ ) (Figure 3D).

Patients with MCI and the *APOE*  $\epsilon 2\epsilon 2$  genotype were not included in the analysis because of the small sample size ( $n = 5$ , of whom 1 was amyloid positive). The prevalence of amyloid pathology in patients with MCI at age 70 years was 89% (95% CI, 81%-94%) for  $\epsilon 4\epsilon 4$  carriers, 66% (95% CI, 60%-72%) for  $\epsilon 3\epsilon 4$  carriers, 57% (95% CI, 35%-76%) for  $\epsilon 2\epsilon 4$  carriers, 35% (95% CI, 31%-40%) for  $\epsilon 3\epsilon 3$  carriers, and 25% (95% CI, 19%-32%) for  $\epsilon 2\epsilon 3$  carriers. Table 4 shows the ORs for amyloid positivity of the *APOE* genotypes relative to the  $\epsilon 3\epsilon 3$  genotype at age 70 years for participants with normal cognition and MCI.

The prevalence of amyloid pathology at the mean age was 5% higher (95% CI, 1% to 8%;  $P = .005$ ) in participants with an education above the median ( $n = 2530$ ) than in those with education below the median ( $n = 2415$ ) regardless of cognitive status, age, and *APOE*- $\epsilon 4$  carrier status (eFigure 1 in the Supplement). There was no significant association with or interaction between sex and any of the risk factors for amyloid positivity (mean difference, 1% [95% CI, -1% to 3%];  $P = .52$ ).

## Comparison With Prevalence of AD-Type Dementia

The age-related increase in amyloid positivity in participants with normal cognition paralleled age-specific AD-type dementia prevalence estimates, with an intervening period of about 20 years (Figure 4A). Similarly, *APOE* genotype-specific estimates of amyloid positivity paralleled *APOE* genotype-specific lifetime risks of AD-type dementia with a difference of 25 to 30 years (Figure 4B).

## Number Needed to Screen

The numbers of participants needed to screen (NNS) to identify 1 amyloid-positive person are displayed according to age, cognitive status, and *APOE* genotype in eTable 6 in the Supplement. The NNS varied from 1.0 (95% CI, 1.0-1.1), for persons with normal cognition or MCI who were older than 70 years with

the *APOE* $\epsilon$ 4 $\epsilon$ 4 genotype, to 16.7 (95% CI, 11.1-25.0), for persons with normal cognition aged 50 years without an *APOE*- $\epsilon$ 4 allele. If *APOE* genotype is unknown, participants need to be screened for this first. The number of participants for whom *APOE* genotyping needs to be performed to find 1 participant with that particular *APOE* genotype who is amyloid positive varied between 3.5 (95% CI, 2.8-4.3), for persons with normal cognition aged 90 years without an *APOE*- $\epsilon$ 4 allele, to 89.6 (95% CI, 64.5-129.0), for persons with normal cognition aged 50 years with the *APOE* $\epsilon$ 4 $\epsilon$ 4 genotype.

## Assessment of Study-Related Heterogeneity

In the total study population, the intraclass correlation coefficient for study-related random intercept variance was 0.085, indicating minor heterogeneity among studies. Within age, *APOE*- $\epsilon$ 4, and diagnostic subgroups, heterogeneity was not substantial according to the  $I^2$  statistic, except for 2 of 54 subgroups (50%-60% in age group 65-69 years of SCI *APOE*- $\epsilon$ 4 carriers and in age group 75-79 years of MCI *APOE*- $\epsilon$ 4 noncarriers) (eTable 7 in the [Supplement](#)).

Visual inspection of variability in prevalence estimates across age in studies with at least 50 participants also indicated that between-study variability was small (eFigure 2 in the [Supplement](#)).

## Post Hoc Analyses

The biomarker used to assess amyloid positivity was not associated with prevalence (mean difference, 0% [95% CI, -7% to 8%];  $P = .87$ ) for participants with normal cognition or MCI ( $n = 6885$ ). Patients with SCI were excluded because amyloid was measured with PET in only 5% of participants. While adjusting for *APOE*- $\epsilon$ 4 carrier status and age, amyloid prevalence at the mean age was higher in patients with amnesic MCI ( $n = 1405$ ) than in patients with nonamnesic MCI ( $n = 225$ , 58% [95% CI, 48% to 67%] vs 47% [95% CI, 35% to 60%], mean difference, 11% [95% CI, 0% to 21%];  $P = .03$ ) and higher in patients with nonamnesic MCI than in participants with normal cognition ( $n = 2289$ , mean difference, 15% [95% CI, 2% to 28%];  $P = .03$ ). The prevalence did not differ between amnesic MCI ( $n = 1405$ ) and MCI patients diagnosed using a broad or unspecified definition of MCI ( $n = 1487$ , mean difference, 3% [95% CI, -6% to 13%];  $P = .51$ ). Prevalence estimates did not differ for published and unpublished studies (eTable 8 in the [Supplement](#)). The prevalence in participants with normal cognition recruited via advertisements ( $n = 1868$ ) was similar to that of participants recruited from hospital departments ( $n = 305$ , mean difference, 4% [95% CI, -13% to 21%];  $P = .96$ ).

## Discussion

This amyloid biomarker study including individuals without dementia provides prevalence estimates of amyloid pathology over an age range of 18 to 100 years for persons with normal cognition, SCI, and MCI. The age at onset of amyloid positivity was associated with cognitive status and the *APOE* genotype. At age 90 years, about 40% of the *APOE*- $\epsilon$ 4 noncarriers and more than 80% of *APOE*- $\epsilon$ 4 carriers with normal cognition were amyloid positive. Amyloid positivity was associated with education but not with sex or

biomarker modality. The age-related prevalence of amyloid positivity in participants with normal cognition paralleled the age-related prevalence of AD-type dementia in the general population in an *APOE* genotype-specific way with a time lag of 20 to 30 years.

Patients with MCI had 20% to 30% higher prevalence estimates of amyloid positivity than those with normal cognition or SCI, supporting the view that MCI is a risk state for AD.<sup>16</sup> Cognitively normal and SCI groups did not differ in amyloid positivity, suggesting that the presence of SCI in a memory clinic population might not be associated with an increased risk for AD. Previous studies in other settings showed inconsistent results regarding differences in amyloid positivity between cognitively normal and SCI participants,<sup>20,21</sup> indicating that further research is needed on this. Patients with nonamnestic MCI had lower prevalence estimates of amyloid positivity than patients with amnestic MCI but higher than participants with normal cognition. This suggests that both amnestic MCI and nonamnestic MCI are associated with an increased risk for AD and that this risk is higher for patients with amnestic MCI. The observation that a substantial number of patients with MCI were not amyloid positive, even at older age, suggests that the MCI phenotype does not always have AD as underlying pathology. Possible non-AD causes in MCI may be hippocampal sclerosis, mild depression, or vascular damage.

Age was a risk factor for amyloid positivity, which is in line with the finding that age is an important risk factor for postmortem amyloid load<sup>22</sup> and for AD-type dementia,<sup>23</sup> as also shown in Figure 4A. The prevalence of amyloid positivity in participants with normal cognition aged 50 to 60 years was somewhat higher than found in an earlier population-based study that was not included in our analysis.<sup>24</sup> This could relate to differences in recruitment strategy and assessment.

Relative to the *APOE*- $\epsilon$ 3 allele, the *APOE*- $\epsilon$ 4 risk allele was associated with a greater risk for amyloid positivity and decreased age at onset, while the *APOE*- $\epsilon$ 2 allele had the opposite associations. This is similar to the relation of *APOE* genotype with the risk for AD-type dementia and age at onset of AD-type dementia as reported in clinical studies<sup>25,26</sup> and the *APOE* genotype-specific lifetime risk for AD as shown in Figure 4B. The high prevalence of amyloid positivity in participants with normal cognition and MCI with  $\epsilon$ 2 $\epsilon$ 4 in the present study indicates that the detrimental relation of amyloid positivity with  $\epsilon$ 4 outweighs the protective association with  $\epsilon$ 2, in line with clinical AD studies.<sup>27</sup> The OR for amyloid pathology of the *APOE* genotypes relative to the  $\epsilon$ 3 $\epsilon$ 3 genotype was similar to the OR for AD-type dementia in case-control studies.<sup>18,27</sup> The strong association of the *APOE* genotype with amyloid positivity emphasizes *APOE* as an important target for treatment studies.<sup>28,29</sup>

Highly educated participants had a higher prevalence of amyloid pathology than those with less formal education. This may seem in contrast with the finding that high education level is associated with a lower risk for AD-type dementia<sup>30</sup> but is in agreement with the cognitive reserve hypothesis.<sup>31</sup> According to this hypothesis, nondemented individuals with a high level of education have a greater cognitive reserve such that they can sustain more amyloid pathology before developing dementia. Education itself was not associated with the extent of pathology at postmortem examination<sup>32</sup> but might modify the relationship

between AD pathology and expression of dementia,<sup>33</sup> resulting in higher amyloid positivity prevalence in nondemented highly educated participants. An alternative explanation would be that highly educated persons with amyloid pathology may be overrepresented in study participation or clinical care seeking due to self-selection bias.

Our finding that the prevalence of amyloid positivity was the same for men and women is in line with a previous neuropathological study showing no difference in neuritic and diffuse plaque load between men and women.<sup>34</sup> This finding is also in agreement with another earlier study,<sup>35</sup> as is our finding that there was no interaction between sex and *APOE*- $\epsilon$ 4 carrier status on amyloid positivity.

Although PET and CSF are thought to measure different types of amyloid- $\beta$ ,<sup>36</sup> we did not find differences in amyloid positivity estimates for PET and CSF biomarkers. This is in line with published high concordance rates of 84% to 92% between the 2 biomarkers.<sup>37,38</sup> Also, high levels of agreement have been reported for studies that provided more than 50 participants to our study in whom amyloid was assessed with both PET and CSF.<sup>39,40</sup>

We pooled data from a large number of studies, and this may have introduced bias because of differences in the methods underlying amyloid assessment, cutoff definition, participant selection, diagnostic criteria, and other aspects of study design. However, in the total study sample; in age, *APOE*, and diagnostic subgroups; and on visual inspection of study-specific prevalences over age, there was limited evidence for study-related heterogeneity, which supports the pooling of data from different studies (eFigure 2 and eTable 7 in the [Supplement](#)). Moreover, the Alzheimer's Association Quality Control program for CSF biomarkers reported that overall concordance for diagnostic classification was high between centers despite analytical variance.<sup>41</sup> We also explored the association of a number of study characteristics with the prevalence in post hoc analyses, but no relation was found. An advantage of participant-level analysis over aggregated pooling is that the power to detect subgroup effects is increased,<sup>42</sup> while the risk for ecological bias is decreased.<sup>43</sup>

A limitation of this study is that our participants with normal cognition were mostly recruited via advertisements, making this sample vulnerable to self-selection bias<sup>44</sup> and restricting generalizability to the general population. Participants with SCI and MCI were mostly recruited from clinical settings, rendering them dissimilar from these individuals in the general population. Participants with significant comorbid disorders are usually excluded from participation, and studies often used standardized cognitive screens, which also affects generalizability. Although MCI was not classified as amnesic or nonamnesic for most participants, our findings indicate that we mostly included amnesic MCI patients because the prevalence estimates in amnesic MCI patients did not differ from those with a broad or unspecified definition of MCI. Still, patients with nonamnesic MCI had a lower prevalence than patients with amnesic MCI, suggesting that this is an important distinction to make in future research. Moreover, our prevalence estimates are based on cross-sectional data. The lifetime risk for individuals without dementia to develop amyloid pathology will be higher than the cross-sectional estimate at any age because amyloid-positive persons may die or progress to dementia at follow-up.

This study has several implications for understanding the development of AD. The observation that key risk factors for AD-type dementia are also risk factors for amyloid positivity in cognitively normal persons provides further evidence for the hypothesis that amyloid positivity in these individuals reflects early AD. Further support for this hypothesis comes from other studies that show that amyloid positivity in nondemented individuals is associated with memory impairment, cognitive decline, increased amyloid deposition and brain atrophy rates, and mortality.<sup>45-48</sup> Our study also indicates that development of AD pathology can start as early as age 30 years, depending on the *APOE* genotype. Comparison with prevalence and lifetime risk estimates of AD-type dementia suggests a 20- to 30-year interval between amyloid positivity and dementia, implying that there is a large window of opportunity to start preventive treatments. Still, the exact interval between the onset of amyloid positivity and onset of AD-type dementia needs to be assessed by long-term follow-up studies because not all persons with amyloid pathology will become demented during their lifetime,<sup>49</sup> and not all individuals with a clinical diagnosis of AD-type dementia have amyloid pathology. Because of the uncertainty about whether and when an amyloid-positive individual without dementia will develop dementia, amyloid positivity in these individuals should not be equated with impending clinical dementia but rather be seen as a risk state. Our prevalence rates can be used as an inexpensive and noninvasive approach to select persons at risk for amyloid positivity.

## Conclusions

Among persons without dementia, the prevalence of cerebral amyloid pathology as determined by PET imaging or CSF findings was associated with age, *APOE* genotype, and presence of cognitive impairment. These findings suggest a 20- to 30-year interval between first development of amyloid positivity and onset of dementia.

## Article Information

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**Corresponding Author:** Willemijn J. Jansen, MSc, Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University, PO Box 616, 6200 MD, Maastricht, the Netherlands ([willemijn.jansen@maastrichtuniversity.nl](mailto:willemijn.jansen@maastrichtuniversity.nl)) and Pieter Jelle Visser, MD, PhD ([pj.visser@maastrichtuniversity.nl](mailto:pj.visser@maastrichtuniversity.nl)).

**Authors/Amyloid Biomarker Study Group** members include the byline authors as well as the following individuals: Pauline Aalten, PhD; Dag Aarsland, MD, PhD; Daniel Alcolea, MD; Myriam Alexander, PhD; Ina S. Almdahl, MD; Steven E. Arnold, MD; Inês Baldeiras, PhD; Henryk Barthel, MD, PhD; Bart N. M. van Berckel, MD, PhD; Kristen Bibeau, PhD; Kaj Blennow, MD, PhD; David J. Brooks, MD, PhD; Mark A. van Buchem, MD, PhD; Vincent Camus, MD, PhD; Enrica Cavedo, MSc; Kewei Chen, PhD; Gael Chetelat, PhD; Ann D. Cohen, PhD; Alexander Drzezga, MD, PhD; Sebastiaan Engelborghs, MD, PhD; Anne M. Fagan, PhD; Tormod Fladby, MD, PhD; Adam S. Fleisher, MD, MAS; Wiesje M. van der Flier, PhD; Lisa Ford, MD; Stefan Förster, MD, PhD; Juan Fortea, PhD; Nadia Foskett, MD, PhD; Kristian S. Frederiksen, MD, PhD; Yvonne Freund-Levi, MD, PhD; Giovanni B. Frisoni, MD; Lutz Froelich, MD, PhD; Tomasz Gabryelewicz, MD,

PhD; Kiran Dip Gill, PhD; Olymbia Gkatzima, MSc; Estrella Gómez-Tortosa, MD, PhD; Mark Forrest Gordon, MD; Timo Grimmer, MD, PhD; Harald Hampel, MD, PhD; Lucrezia Hausner, MD, PhD; Sabine Hellwig, MD; Sanna-Kaisa Herukka, MD, PhD; Helmut Hildebrandt, PhD; Lianna Ishihara, PhD; Adrian Ivanoiu, MD, PhD; William J. Jagust, MD; Peter Johannsen, MD, PhD; Ramesh Kandimalla, PhD; Elisabeth Kapaki, MD, PhD; Aleksandra Klimkowicz-Mrowiec, MD, PhD; William E. Klunk, MD, PhD; Sebastian Köhler, PhD; Norman Koglin, PhD; Johannes Kornhuber, MD; Milica G. Kramberger, MD, PhD; Koen Van Laere, MD, PhD, DrSc; Susan M. Landau, PhD; Dong Young Lee, MD, PhD; Mony de Leon, EdD; Viviana Lisetti, MSc; Alberto Lleó, MD, PhD; Karine Madsen, MD, PhD; Wolfgang Maier, MD, PhD; Jan Marcusson, MD, PhD; Niklas Mattsson, MD, PhD; Alexandre de Mendonça, MD, PhD; Olga Meulenbroek, PhD; Philipp T. Meyer, MD, PhD; Mark A. Mintun, MD, MD; Vincent Mok, MD; José Luis Molinuevo, MD, PhD; Hanne M. Møllergård, PhD; John C. Morris, MD; Barbara Mroczko, MD, PhD; Stefan Van der Mussele, PhD; Duk L. Na, MD, PhD; Andrew Newberg, MD, PhD; Agneta Nordberg, MD, PhD; Arto Nordlund, PhD; Gerald P. Novak, MD; George P. Paraskevas, MD, PhD; Lucilla Parnetti, MD, PhD; Gayan Perera, PhD; Oliver Peters, MD; Julius Popp, MD; Sudesh Prabhakar, MD, PhD; Gil D. Rabinovici, MD; Inez H. G. B. Ramakers, PhD; Lorena Rami, MSc; Catarina Resende de Oliveira, MD, PhD; Juha O. Rinne, MD, PhD; Karen M. Rodrigue, PhD; Eloy Rodríguez-Rodríguez, MD, PhD; Catherine M. Roe, PhD; Uros Rot, MD, PhD; Christopher C. Rowe, MD, PhD; Eckart Rütger, MD, PhD; Osama Sabri, MD, PhD; Pascual Sanchez-Juan, MD, PhD; Isabel Santana, MD, PhD; Marie Sarazin, MD, PhD; Johannes Schröder, MD, PhD; Christin Schütte, MSc; Sang W. Seo, MD, PhD; Femke Soetewey, MSc; Hilka Soininen, MD, PhD; Luiza Spuru, MD, PhD; Hanne Struyfs, MSc; Charlotte E. Teunissen, PhD; Magda Tsolaki, MD, PhD; Rik Vandenberghe, MD, PhD; Marcel M. Verbeek, PhD; Victor L. Villemagne, MD, PhD; Stephanie J. B. Vos, PhD; Linda J. C. van Waalwijk van Doorn, MSc; Gunhild Waldemar, MD, DMSc; Anders Wallin, MD, PhD; Åsa K. Wallin, MD, PhD; Jens Wiltfang, MD, PhD; David A. Wolk, MD; Marzena Zboch, MD, PhD; Henrik Zetterberg, MD, PhD.

**Affiliations of Authors/Amyloid Biomarker Study Group:** Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University, Maastricht, the Netherlands (Aalten, Köhler, Ramakers, Vos); Department of Neurology and Alzheimer Center, VU University Medical Center, Neuroscience Campus Amsterdam, Amsterdam, the Netherlands (van der Flier); Department of Radiology and Nuclear Medicine, VU University Medical Center, Neuroscience Campus Amsterdam, Amsterdam, the Netherlands (van Berckel); Department of Neurology, Memory and Aging Center, University of California, San Francisco (Rabinovici); Helen Wills Neuroscience Institute, University of California, Berkeley (Jagust, Landau); Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, the Netherlands (van der Flier); Center for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway (Aarsland); Neurology Department, Hospital de Sant Pau, Barcelona, Spain (Alcolea, Fortea, Lleó); Roche Products, Welwyn Garden City, United Kingdom (Alexander, Foskett, Perera); Department of Neurology, Akershus University Hospital, Lørenskog, Norway (Almdahl, Fladby, Møllergård); Department of Neurology, University of Pennsylvania, Philadelphia (Arnold, Wolk); Center for Neuroscience and Cell Biology, Faculty of Medicine, Hospital Center University of Coimbra, Portugal (Baldeiras, Resende de Oliveira, Santana); Department of Nuclear Medicine, University of Leipzig, Leipzig, Germany (Barthel,

Sabri); GlaxoSmithKline, Worldwide Epidemiology, Research Triangle Park, North Carolina (Bibeau); Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Mölndal, Sweden (Blennow, Nordlund, A. Wallin, Zetterberg); Division of Neuroscience, Medical Research Council Clinical Sciences Centre, Imperial College London, London, United Kingdom (Brooks); Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands (van Buchem); CHRU de Tours, CIC INSERM 1415, INSERM U930, and Université François Rabelais de Tours, Tours, France (Camus); Laboratory of Epidemiology, Neuroimaging and Telemedicine, IRCCS San Giovanni di Dio Fatebenefratelli, Brescia, Italy (Cavedo, Frisoni); Sorbonne University, University Pierre et Marie Curie, Paris 06, Institut de la Mémoire et de la Maladie d'Alzheimer (IM2A) and Institut du Cerveau et de la Moelle épinière (ICM), UMR S 1127, Hôpital de la Pitié-Salpêtrière Paris and CATI Multicenter Neuroimaging Platform, Paris, France (Cavedo); Banner Alzheimer's Institute, Phoenix, Arizona (Chen, Fleisher); Institut National de la Santé et de la Recherche Médicale (Inserm), U1077, Caen, France (Chetelat); University of Pittsburgh School of Medicine, Department of Psychiatry, Pittsburgh, Pennsylvania (Cohen, Klunk); Department of Nuclear Medicine, University of Cologne, Cologne, Germany (Drzezga); Reference Center for Biological Markers of Dementia (BIODEM), University of Antwerp, Antwerp, Belgium (Engelborghs, Van der Mussele, Soetewey, Struyfs); Knight Alzheimer's Disease Research Center, Department of Neurology, Washington University School of Medicine, St Louis, Missouri (Fagan, Morris, Roe); Eli Lilly, Indianapolis, Indiana (Fleisher); Department of Neurosciences, University of California, San Diego (Fleisher); Janssen Research and Development, Titusville, New Jersey (Ford, Novak); Department of Nuclear Medicine, Technischen Universitaet München, Munich, Germany (Förster); Memory Clinic, Danish Dementia Research Center, Rigshospitalet, Copenhagen, Denmark (Johannsen); Department of Geriatrics, Institution of NVS, Section of Clinical Geriatrics, Karolinska Institutet, Stockholm, Sweden (Freund-Levi); Department of Geriatric Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany (Froelich, Hausner); Department of Neurodegenerative Disorders, Mossakowski Medical Research Centre Polish Academy of Sciences, Warsaw, Poland (Gabryelewicz); Postgraduate Institute of Medical Education and Research (PGIMER), Department of Biochemistry, Research Block-A, Chandigarh, India (Gill, Kandimalla); Third Department of Neurology, Aristotle University of Thessaloniki, Thessaloniki, Greece (Gkatzima, Tsolaki); Department of Neurology, Fundación Jiménez Díaz, Madrid, Spain (Gómez-Tortosa); Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut (Gordon); Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar der Technischen Universitaet München, Munich, Germany (Grimmer); AXA Research Fund and UPMC Chair Sorbonne Universités, Université Pierre et Marie Curie, Paris 06, Institut de la Mémoire et de la Maladie d'Alzheimer and INSERM U1127, Institut du Cerveau et de la Moelle épinière (ICM), Département de Neurologie, Hôpital de la Pitié-Salpêtrière, Paris, France (Hempel); Department of Psychiatry, Alzheimer Memorial Center and Geriatric Psychiatry Branch, Ludwig-Maximilian University, Munich, Germany (Hempel); Center of Geriatrics and Gerontology, University Hospital Freiburg, Freiburg, Germany (Hellwig); Center for Neurology, Hospital of Bremen-Ost, Bremen, Germany (Hildebrandt, Schütte); GlaxoSmithKline, Worldwide Epidemiology, Epidemiology, Genetic Epidemiology and Neurology, United Kingdom (Ishihara); Memory Clinic and Neurochemistry Laboratory, Saint Luc University Hospital, Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium (Ivanoiu); Radiation Oncology,

Emory University, Atlanta, Georgia (Kandimalla); First Department of Neurology, Neurochemistry Unit and Cognitive and Movement Disorders Clinic, National and Kapodistrian University of Athens, Eginition Hospital, Athens, Greece (Kapaki, Paraskevas); Jagiellonian University College of Medicine, Krakow, Poland (Klimkowicz-Mrowiec); Piramal Imaging, Berlin, Germany (Koglin); Department of Psychiatry and Psychotherapy, Friedrich-Alexander University of Erlangen-Nuremberg, Erlangen, Germany (Kornhuber); Center for Cognitive Impairments, University Medical Centre Ljubljana, Ljubljana, Slovenia (Kramberger, Rot); Laboratory for Cognitive Neurology and Alzheimer Research Centre KU Leuven, Catholic University Leuven, Leuven, Belgium (Vandenberghe); Department of Neuropsychiatry, Seoul National University, College of Medicine, Seoul, South Korea (Lee); School of Medicine, Center for Brain Health, New York University, New York (de Leon); Section of Neurology, Center for Memory Disturbances, University of Perugia, Perugia, Italy (Lisetti, Parnetti); Neurobiology Research Unit, Copenhagen University Hospital, Copenhagen, Denmark (Madsen); Department of Psychiatry and Psychotherapy, University of Bonn, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany (Maier); Geriatric Medicine, Department of Clinical and Experimental Medicine, University of Linköping, Linköping, Sweden (Marcusson); Institute of Molecular Medicine and Faculty of Medicine, University of Lisbon, Portugal (de Mendonça); Department of Geriatric Medicine, Radboud Alzheimer Center, Radboud University Medical Center, Nijmegen, the Netherlands (Meulenbroek); Department of Nuclear Medicine, University Hospital Freiburg, Freiburg, Germany (Meyer); Avid Radiopharmaceuticals, Philadelphia, Pennsylvania (Mintun); Lui Che Woo Institute of Innovative Medicine, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China (Mok); Alzheimer's Disease and Other Cognitive Disorders Unit, IDIBAPS, Clinic University Hospital, Barcelona, Spain (Molinuevo, Rami); Department of Neurodegeneration Diagnostics, Leading National Research Centre in Białystok (KNOW), Medical University of Białystok, Białystok, Poland (Mroczko); Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea (Na, Seo); Myrna Brind Center of Integrative Medicine, Thomas Jefferson University and Hospital, Philadelphia, Pennsylvania (Newberg); Dept NVS, Center for Alzheimer, Translational Alzheimer Neurobiology, Karolinska Institutet, and Geriatric Medicine, Karolinska University Hospital, Stockholm, Sweden (Nordberg); Department of Psychological Medicine, Institute of Psychiatry, Kings College London, London, United Kingdom (Perera); Department of Psychiatry and Psychotherapy, Charité Berlin, German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany (Peters); Department of Psychiatry, Service of Old Age Psychiatry and Department of Clinical Neurosciences, Leenaards Memory Centre, University Hospital of Lausanne, Lausanne, Switzerland (Popp); Postgraduate Institute of Medical Education and Research (PGIMER), Department of Neurology, Nehru Hospital, Chandigarh, India (Prabhakar); Turku PET Centre and Division of Clinical Neurosciences Turku, University of Turku and Turku University Hospital, Turku, Finland (Rinne); Center for Vital Longevity, University of Texas at Dallas (Rodrigue); Neurology Service, University Hospital Marqués de Valdecilla, IDIVAL, Santander, Spain (Rodríguez-Rodríguez, Sanchez-Juan); Department of Nuclear Medicine and Centre for PET, Austin Health, Melbourne, Australia (Rowe, Villemagne); Department of Psychiatry and Psychotherapy, University Medical Center, Georg-August University, Göttingen, Germany (Rüther, Wiltfang); Neurologie de la Mémoire et du Langage, Centre Hospitalier Sainte-Anne, Université Paris 5, Paris, France (Sarazin); Sektion Gerontopsychiatrie, Universität

Heidelberg, Heidelberg, Germany (Schröder); Department of Neurology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland (Herukka, Soininen); Department of Geriatrics-Gerontology-Gerontopsychiatry, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania (Spiru); Neurochemistry Laboratory and Biobank, Department of Clinical Chemistry, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, the Netherlands (Teunissen); Departments of Neurology and Laboratory Medicine, Donders Institute for Brain, Cognition and Behaviour, Radboud Alzheimer Center, Radboud University Medical Center, Nijmegen, the Netherlands (Verbeek, van Waalwijk van Doorn); Danish Dementia Research Center, Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark (Frederiksen, Waldemar); Clinical Memory Research Unit, Clinical Sciences Malmö, Lund University, Lund, Sweden (Mattsson, Å. K. Wallin); Alzheimer Center, Wrocław Medical University, Ścinawa, Poland (Zboch); UCL Institute of Neurology, Queen Square, London, United Kingdom (Zetterberg); Memory Clinic and LANVIE-Laboratory of Neuroimaging of Aging, University Hospitals, and University of Geneva, Geneva, Switzerland (Frisoni); Department of Imaging and Pathology, Catholic University Leuven, Leuven, Belgium (Van Laere).

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*Study concept and design:* Jansen, Ossenkuppele, Verhey, Visser.

*Acquisition, analysis, or interpretation of data:* All authors.

*Drafting of the manuscript:* Jansen, Visser.

*Critical revision of the manuscript for important intellectual content:* All authors.

*Statistical analysis:* Jansen, Knol, Visser.

*Administrative, technical, or material support:* All authors.

*Study supervision:* Visser.

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received speaker and consultant honoraria as well as travel expenses from Piramal Imaging (Berlin) and personal fees from Siemens Healthcare. Dr Bibeau reported being a share-holding employee of GlaxoSmithKline. Dr Blennow reported having received personal fees (advisory board) from Roche Diagnostics, IBL International, Novartis, and Eli Lilly. Dr Brooks reported having served as consultant for GE Healthcare. Dr Camus reported having received grants from the French Ministry of Health. Dr Chen reported having received grants from the National Institutes of Health (NIH). Dr Drzezga reported having received speaker honoraria and consulting fees from GE Healthcare, AVID/Lilly, and Piramal. Dr Fagan reported having received grants from NIH, Fred Simmons and Olga Mohan, and Charles and Joanne Knight Alzheimer's Research Initiative of the Washington University Knight Alzheimer's Disease Research Center; having received personal fees from IBL International, Roche, and AbbVie; and having a patent, 6,465,195 B2, "Predictive diagnostic for Alzheimer's disease," issued and a patent, PCT/US09/050255, "A risk factor and new therapeutic target for Alzheimer's disease," pending. Dr Fladby reported having a patent "Methods and compositions for monitoring phagocytic activity," PCT/US2011/062233, pending. Dr Fleisher reported having been a full-time employee of the Banner Alzheimer's Institute; being a full-time employee of Eli Lilly; maintaining a voluntary faculty appointment at the University of California, San Diego; having been a member of data and safety monitoring boards for Merck, Pfizer, and the National Institute of Aging (NIA); having received grant funding from NIA and Avid Radiopharmaceutical; and having been a consultant for Eli Lilly, Grifols, Avid Radiopharmaceuticals, and Siemens Imaging. Dr van der Flier reported having received grants from Boehringer Ingelheim, Piramal Imaging, and Roche. Dr Förster reported having received personal fees (consultancy) from Piramal, Bayer, and GE. Dr Foskett reported being a full-time employee of Roche Prod and holding Roche shares and share options. Dr Frisoni reported having received grants and/or personal fees from Lilly, Bristol-Myers Squibb, Bayer, Lundbeck, Elan, AstraZeneca, Pfizer, Taurx, Wyeth, GE, Baxter, Avid, Roche, Piramal, and the Alzheimer's Association. Dr Gill reported having received grants from the Indian Council of Medical Research, New Delhi, India. Dr Gordon reported being a salaried employee of Boehringer Ingelheim Pharmaceuticals. Dr Grimmer reported having received personal fees from Eli Lilly. Dr Hampel reported having received grants, personal fees, and/or nonfinancial support from Boehringer-Ingelheim, Bristol-Myers Squibb, Elan, Novartis, Eisai, Pfizer, sanofi-aventis, Roche Pharmaceuticals and Diagnostics, GE Healthcare, Avid, Eli Lilly, GlaxoSmithKline Biologicals, Jung-Diagnostics, and Cytos and having a patent, "Method for predicting whether subjects with mild cognitive impairment (MCI) will develop Alzheimer's disease," pending; a patent, "3-Hydroxykynurenin im Serum als diagnostischer Marker für die Demenz vom Alzheimer-Typ," pending; a patent, "Neurodegenerative markers for psychiatric conditions," pending; a patent, "Ratio A $\beta$ 42/40 im Plasma in der Früh- und Differentialdiagnose der Alzheimer Krankheit," pending; a patent "Liquordiagnostisches in vitro Verfahren zur Diagnose von Demenz Erkrankungen und neuroinflammatorischen Erkrankungen," pending; and a patent, "In vitro Verfahren zur Diagnose von neurodegenerativen Erkrankungen," pending. Dr Hellwig reported having received grants from GE Healthcare and Medical Faculty, University of Freiburg. Dr Ishihara reported being an employee and shareholder of GlaxoSmithKline. Dr Jagust reported having received personal fees from Banner Alzheimer Institute/Genentech, Synarc/Bioclinica, and Novartis. Dr Kandimalla reported having received grants from the Indian Council of Medical Research, India. Dr Kapaki reported having received

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**Correction:**This article was corrected online May 19, 2015, to fix curves in Figure 3C.

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